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(21) International Application Number: PCT/NL94/00239 (22) International Filing Date: 3 October 1994 (03.10.94) (30) Priority Data: 107,167 3 October 1993 (03.10.93) IL (71) Applicant (for all designated States except US): KNOWHOW LICENSING & KNOWHOW TRANSFER B.V. [NL/NL]; 7th floor, Haaksbergweg 55, NL-1101 BR Amsterdam (NL). (72) Inventor; and (75) Inventor/Applicant (for US only): LURIE, Raziël [IL/IL]; 33 Mishmeret Street, 69694 Tel Aviv (IL). (74) Agent: DE BRUIJN, Leendert C.; Nederlandsch Octrooibureau, P.O. Box 29720, Scheveningseweg 82, NL-2502 LS The Hague (NL).			(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: MEDICAMENTS COMPRISING RELAXIN AND THEIR USE			
(57) Abstract Use of relaxin in the manufacture of a medicament for the treatment and prevention of a condition selected from cutaneous aging, androgenetic alopecia and related conditions.			

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1 MEDICAMENTS COMPRISING RELAXIN AND THEIR USE

2 FIELD AND BACKGROUND OF THE INVENTION

3 The present invention relates to use of relaxin in
4 the manufacture of medicaments having a novel applica-
5 tion, to a method in which relaxin is utilized for the
6 treatment and prevention of certain conditions and to
7 pharmaceutical compositions comprising relaxin.

8 Relaxin otherwise known as Cervilaxin, and formerly
9 referred to as Releasin, is a polypeptide hormone secret-
10 ed by the corpora lutea of many mammalian species during
11 pregnancy.

12 As described e.g. in U.S. Patent No. 3,096,246, the
13 contents of which are incorporated herein by reference,
14 relaxin is present in the ovaries of animals and may be
15 extracted therefrom. It is believed to be a hormone of
16 pregnancy and has aroused great interest in the field of
17 medical research. For instance, it has been known to
18 cause uterine cervix relaxation in cows; to increase the
19 dilatability of the uterine cervix in ovariectomized
20 estrogen-primed hogs; to cause definite milk let-down in
21 sheep, and, to a lesser extent, in cows, and to cause
22 marked lobulo-alveolar growth of the mammary gland in
23 rats; and, in the clinic, it has been found to cause
24 dilation of the uterine cervix in near-term pregnant
25 women who fail to dilate after injections of pitocin, and
26 to stop premature labor in certain female patients,
27 allowing them to go to term.

28 EP 08664g, the contents of which are incorporated
29 herein by reference, relates to the molecular cloning and
30 characterization of the gene sequence coding for porcine
31 relaxin. Thus, recombinant DNA techniques for the prepa-
32 ration of porcine relaxin were described more than ten
33 years ago. However, before the advent of the present
34 invention application of relaxin has been restricted
35 essentially to pregnancy- and gynecologically-related
36 uses.

1 SUMMARY OF THE INVENTION

2 It has now been found in accordance with the present
3 invention that relaxin can be used to treat and prevent
4 cutaneous aging, androgenetic alopecia and related condi-
5 tions, and thus to encourage hair growth and to prevent
6 hair loss.

7 Thus in one aspect, the invention provides use of
8 relaxin in the manufacture of a medicament for the treat-
9 ment and prevention of a condition selected from cutane-
10 ous aging, androgenetic alopecia and related conditions,
11 e.g., atrophy, sclerosis and miniaturization of the hair
12 and hair follicles. The medicament may comprise relaxin
13 in combination with a pharmaceutically acceptable, e.g.
14 topically acceptable, carrier, and may be used, for
15 example, for prolonging the duration of the anagen stage
16 of hair growth.

17 In another aspect, the invention provides a method
18 for the treatment and prevention of a condition selected
19 from cutaneous aging, androgenetic alopecia and related
20 conditions, which comprises administering to a human in
21 which said treatment or prevention is desired, an effec-
22 tive amount of relaxin. In this method, relaxin may be
23 administered in combination with a pharmaceutically
24 acceptable (e.g. a topically acceptable) carrier. The
25 method may thus be used, e.g., for the treatment and
26 prevention of a condition selected from atrophy, sclero-
27 sis and miniaturization of the hair and hair follicles,
28 or for prolonging the duration of the anagen stage of
29 hair growth.

30 In yet another aspect, the invention provides a
31 pharmaceutical composition for the treatment and preven-
32 tion of a condition selected from cutaneous aging, andro-
33 genetic alopecia and related conditions, which comprises
34 relaxin in combination with a pharmaceutically acceptable
35 carrier, e.g. a topically acceptable carrier.

36

1 DETAILED DESCRIPTION OF THE INVENTION

2 As is known, the cyclic activity of the hair is
3 divided into three stages: a period of active growth
4 known as anagen, a short transition phase called catagen,
5 and a resting period which ends in hair loss, called
6 telogen.

7 It is also an accepted fact that the percentage of
8 follicles in anagen rises steeply during pregnancy, when
9 as many as 95% of the follicles are active. Two to four
10 months after parturition, the proportion falls to less
11 than 70%. Thus it appears that the hormonal conditions of
12 late pregnancy prolong anagen, and follicles are conse-
13 quently precipitated into telogen via catagen after
14 parturition.

15 Androgenetic alopecia (AA), which is also called
16 common baldness, or male pattern baldness, independent of
17 its causes, is the cutaneous aging of a particular zone,
18 the scalp. AA can be defined, on one hand, as atrophy,
19 sclerosis or miniaturization of the hair follicle, and on
20 the other hand, a progressive shortening of the average
21 duration of the anagen stage, which results in vellus
22 hair prior to complete disappearance.

23 The dermal papilla is a connective tissue structure
24 situated at the base of the hair follicle. In anagen
25 follicles, the papilla invaginates the epithelial hair
26 bulb matrix, remaining in contact with the fibrous sheath
27 surrounding the follicle via a narrow stalk at its base.

28 The papilla is composed of specialized fibroblast-
29 like cells and the root sheath contains fibroblast popu-
30 lation. The dermal papilla plays a fundamental role in
31 induction, maintenance and regulation of hair growth.

32 During anagen, the papilla cells lie in an extracel-
33 lular matrix rich in mucopolysaccharides and basement
34 membrane proteins and display ultra-structural features
35 indicative of synthetic activity. The extracellular
36 matrix gradually diminishes during catagen and disappears

1 almost completely during telogen. It is now generally
2 accepted that fibroblasts are responsible for the manu-
3 facture of all the dermal connective tissue elements or
4 their precursors, i.e., ground substance, collagen and
5 elastin.

6 Relaxin influences the fibroblasts and fibroblast
7 -like cells of the pilosebaceous unit. Relaxin treatment,
8 either topically or systematically, will result in pre-
9 venting atrophy, sclerosis and miniaturization of the
10 hair, by prolonging the duration of the anagen stage, or
11 otherwise. It will remodulate the aging process in gener-
12 al and in particular the AA in male and female.

13 Thus, according to the present invention, there is
14 provided a composition which can be applied topically in
15 lotion, gel or cream form, or systematically for internal
16 or parenteral use, in the form of capsules, tablets or
17 ampules, for treatment of androgenetic alopecia and
18 related conditions such as alopecia areata, anagen efflu-
19 vium, telogen post-partum alopecia, diffuse alopecia, and
20 alopecia androgenica.

21 Similarly, the composition of the present invention
22 could be used in the prevention and treatment of cutane-
23 ous aging in areas other than the scalp.

24 Said compositions can be in the form of creams,
25 lotions, ointments or gels, prepared for use in any
26 conventional manner, in admixture with one or more physi-
27 ologically acceptable carriers and diluents.

28 The compositions may take such forms as suspension,
29 solutions, or emulsions in oily or aqueous vehicles, and
30 may contain formulatory agents such as emulsifying,
31 suspending, stabilizing, gelling and/or dispersing
32 agents.

33 Alternatively, the active ingredients may be in
34 powder form for constitution with a suitable vehicle,
35 e.g., sterile, pyrogen-free water, free water, before
36 use.

1 While it is possible for the active ingredients to
2 be administered alone, it is preferable to present them
3 as pharmaceutical formulations. The formulations of the
4 present invention comprise at least one active ingredi-
5 ent, as above defined, together with one or more accept-
6 able carriers therefor and optionally other therapeutic
7 ingredients. The carrier (s) must be acceptable in the
8 sense of being compatible with the other ingredients of
9 the formulation and not deleterious to the recipient
10 thereof.

11 The formulations may conveniently be presented in
12 unit dosage form and may be prepared by any of the meth-
13 ods well known in the art of pharmacy. Such methods
14 include the step of bringing into association the active
15 ingredient with the carrier, which constitutes one or
16 more accessory ingredients. In general, the formulations
17 are prepared by uniformly and intimately bringing into
18 association the active ingredient with liquid carriers or
19 finely divided solid carriers, or both, and then, if
20 necessary, shaping the product.

21 The formulations are preferably applied as a topical
22 lotion, gel or cream, containing the active ingredient in
23 a concentration of, for example, 0.005 % - 10.0%, prefer-
24 ably 0.01% - 5.0% w/w and most preferably 0.05% - 2% w/w.
25 When formulated in a cream, the active ingredients may be
26 employed with an oil-in-water cream base.

27 If desired, the aqueous phase of the cream base may
28 include, for example, at least 30 % w/w of a polyhydric
29 alcohol, i.e., an alcohol having two or more hydroxyl
30 groups such as propylene glycol, butane-1,3-diol, manni-
31 tol, sorbitol, glycerol and polyethylene glycol and
32 mixtures thereof. The topical formulations may desirably
33 include compound which enhances absorption or penetration
34 of the active ingredient through the skin or other af-
35 fected areas. Examples of such dermal penetration enhanc-
36 ers include dimethylsulphoxide and related analogues.

1 The oily phase of the emulsions of this invention
2 may be constituted from known ingredients in a known
3 manner.

4 While the phase may comprise merely an emulsifier
5 (otherwise known as an emulgent), it desirably comprises
6 a mixture of at least one emulsifier with a fat or an oil
7 or with both a fat and an oil. Preferably, a hydrophilic
8 emulsifier is included together with a lipophilic emulsi-
9 fier, which acts as a stabilizer. It is also preferred to
10 include both an oil and a fat. Together, the
11 emulsifier(s), with or without stabilizer(s), make up the
12 so-called emulsifying wax, and the wax, together with the
13 oil and/or fat, make up the so-called emulsifying oint-
14 ment base, which forms the oily dispersed phase of the
15 cream formulations.

16 Emulgents and emulsion stabilizers suitable for use
17 in the formulation of the present invention include Tween
18 60, Span 80, cetostearyl alcohol, myristyl alcohol,
19 glyceryl mono-stearate and sodium lauryl sulphate.

20 The choice of suitable oils or fats for the formula-
21 tion is based on achieving the desired cosmetic proper-
22 ties, since the solubility of the active compound in most
23 oils likely to be used in pharmaceutical emulsion formu-
24 lations is very low. Thus, the cream should preferably be
25 a non-greasy, non-staining and washable product with
26 suitable consistency to avoid leakage from tubes or other
27 containers. Straight or branched chain, mono- or dibasic
28 alkyl esters such as di-isoadipate, isocetyl stearate,
29 propylene glycol diester or coconut fatty acids, isopro-
30 pyl myristate, decyl oleate, isopropyl palmitate, butyl
31 stearate, 2-ethylhexyl palmitat, or a blend of branched
32 chain esters known as Crodamol CAP may be used, the last
33 three being preferred esters. These may be used alone or
34 in combination, depending on the properties required.
35 Alternatively, high melting-point lipids, such as white
36 soft paraffin and/or liquid paraffin, or other mineral

1 oils, can be used.

2 While the invention will now be described in connec-
3 tion with certain preferred embodiments in the following
4 examples so that aspects thereof may be more fully under-
5 stood and appreciated, it is not intended to limit the
6 invention to these particular embodiments. On the con-
7 trary, it is intended to cover all alternatives, modifi-
8 cations and equivalents as may be included within the
9 scope of the invention as defined by the appended claims.
10 Thus, the following examples which include preferred
11 embodiments will serve to illustrate the practice of this
12 invention, it being understood that the particulars shown
13 are by way of example and for purposes of illustrative
14 discussion of preferred embodiments of the present inven-
15 tion only and are presented in the cause of providing
16 what is believed to be the most useful and readily under-
17 stood description of formulation procedures as well as of
18 the principles and conceptual aspects of the invention.

19

20 Example 1 - Lotion

21	Relaxin	100 mg
22	Deionized water	850 ml
23	Ethanol	150 ml

24 The Relaxin was dissolved in the mixture of solvents.

25

26 Example 2 - Gel

27	Relaxin	20 mg
28	Deionized water	49.0 g
29	Ethanol	49.0 g
30	Carbomer 934 P	0.5 g
31	Triethanolamine	0.5 g

32

33 The Relaxin was dissolved in the water/alcohol mixture.
34 The carbomer was dispersed in the solution and the trie-
35 thanolamine was added while agitating constantly.

36

1 Example 3 - Gel

2	Relaxin	5.0 mg
3	Deionized water	83.9 g
4	Ethanol	75.0 g
5	Carbomer 934 P	0.25 g
6	HPMC 4000 cps	0.60 g
7	Triethanolamine	0.25 g

8

9 The Relaxin and HPMC were dissolved in the water and the
10 alcohol was added. The carbomer was dispersed in the
11 solution and triethanolamine was added while agitating.

12

13 Example 4 - Cream

14	Relaxin	1.0 g
15	Cetylester wax	2.0 g
16	Polysorbate 60	1.0 g
17	Paraffin oil	10.0 g
18	Carbomer 934 P	1.0 g
19	Glycerol	5.0 g
20	Potassium sorbate	0.2 g
21	Ammonia 25%	0.7 g
22	Deionized water	to 100 g

23

24 The Relaxin, potassium sorbate, and glycerol were dis-
25 solved in water and the carbomer was dispersed in the
26 solution, at room temperature. The cetylester wax, poly-
27 sorbate and paraffin oil were heated to dissolve, and
28 were mixed with the aqueous portion at room temperature.
29 Ammonia was added to gel the carbomer.

30

31 Example 5 - Tablets

32 Quantities per tablet:

33	Relaxin	100 mg
34	Lactose	180 mg
35	Polyvinylpyrrolidone	10.0 mg
36	Sodium starch glycollate	7.5 mg

1 Magnesium stearate 1.25 mg
2 The Relaxin and the polyvinylpyrrolidone were dissolved
3 in a quantity of dionized water and the lactose and
4 sodium starch glycollate were granulated in accordance
5 with normal procedure. The granulation was dried and the
6 magnesium stearate added. The mixture was compressed into
7 tablets.

8

9 Example 6 - Capsules

10 Quantities per capsule:

11 Relaxin 200 mg

12 Microcrystalline cellulose 100 mg

13 Colloidal silicon dioxide 3 mg

14 The ingredients were thoroughly blended and filled into
15 hard gelatin capsules.

16

17 Example 7 - Ampoules or Multidose Ampoules

18

19 Relaxin 50 mg

20 Benzyl alcohol 20 mg

21 Water for injection to 1 ml

22 The ingredients were dissolved in the water for injection
23 and the solution sterilized by filtration. The ampoules
24 were filled and sealed under aseptic conditions.

25

26 Example 8 - Implant

27

28 Relaxin 200 mg

29 In a suitable non-toxic medium, e.g., silicon polymer, to
30 act as an embedding agent.31 Example 9 - Slow Release Patch

32

33 Relaxin 500 mg

34 This is spread onto a polyester layer with an adhesive
35 such as polyiso butylene, and covered with a siliconized
36 polyester release liner.

1

2 Example 10 - Shampoo

3	Relaxin	2.0 g
4	Sodium lauryl ether sulphate	30.0 g
5	Diethanolamine of coconut oil fatty acids	6.0 g
6	Water	62.0 g

7

8 It will be evident to those skilled in the art that
9 the invention is not limited to the details of the fore-
10 going illustrative examples and that the present inven-
11 tion may be embodied in other specific forms without
12 departing from the essential attributes thereof, and it
13 is therefore desired that the present embodiments and
14 examples be considered in all respects as illustrative
15 and not restrictive, reference being made to the appended
16 claims, rather than to the foregoing description, and all
17 changes which come within the meaning and range of equiv-
18 alency of the claims are therefore intended to be em-
19 braced therein.

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CLAIMS

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3 1. Use of relaxin in the manufacture of a medicament for
4 the treatment and prevention of a condition selected from
5 cutaneous aging, androgenetic alopecia and related condi-
6 tions.
7
- 8 2. Use according to claim 1, wherein said medicament
9 comprises relaxin in combination with a pharmaceutically
10 acceptable carrier.
11
- 12 3. Use according to claim 2, wherein said pharmaceutical-
13 ly acceptable carrier is a topically acceptable carrier.
14
- 15 4. Use according to claim 1, for the manufacture of a
16 medicament for the treatment and prevention of a condi-
17 tion selected from atrophy, sclerosis and miniaturization
18 of the hair and hair follicles.
19
- 20 5. Use according to claim 1, for the manufacture of a
21 medicament for prolonging the duration of the anagen
22 stage of hair growth.
23
- 24 6. Method for the treatment and prevention of a condition
25 selected from cutaneous aging, androgenetic alopecia and
26 related conditions, which comprises administering to a
27 human in which said treatment or prevention is desired,
28 an effective amount of relaxin.
29
- 30 7. Method according to claim 6, wherein relaxin is admin-
31 istered in combination with a pharmaceutically acceptable
32 carrier.
33
- 34 8. Method according to claim 7, wherein said pharmaceuti-
35 cally acceptable carrier is a topically acceptable carri-
36 er.

- 1
2 9. Method according to claim 6, for the treatment and
3 prevention of a condition selected from atrophy, sclero-
4 sis and miniaturization of the hair and hair follicles.
5
6 10. Method according to claim 6, for prolonging the
7 duration of the anagen stage of hair growth.
8
9 11. Pharmaceutical composition for the treatment and
10 prevention of a condition selected from cutaneous aging,
11 androgenetic alopecia and related conditions, which
12 comprises relaxin in combination with a pharmaceutically
13 acceptable carrier.
14
15 12. Pharmaceutical composition according to claim 11,
16 wherein said pharmaceutically acceptable carrier is a
17 topically acceptable carrier.
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/NL 94/00239

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K38/22 //A61K7/06, A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INDIAN JOURNAL OF DERMATOLOGY AND VENERELOGY, vol.39, no.5, 1973, BOMBAY, INDIA pages 199 - 202 R.N. SHAH ET AL. 'A CASE REPORT OF GENERALISED MORPHEA.' see page 201, right column, line 17 - page 202, right column, line 32; figures 1,2 ---	1-12
X	CH,A,661 662 (G.L. FLOERSHEIM) 14 August 1987 see page 2, right column, line 46 - line 63; claims see page 3, left column, line 12 - line 15 see page 3, left column, line 34 - line 45 see page 3, right column, line 8 - line 30 --- -/--	1-4,6-9, 11,12



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Patent family members are listed in annex.

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THE CANADIAN MEDICAL ASSOCIATION JOURNAL, vol.78, no.12, 15 June 1958, OTTAWA, CA pages 935 - 941 R.X. SANDS 'RELAXIN-A CLINICAL REVIEW.' see page 937, right column, line 32 - page 938, left column, line 60 -----	1-12

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH-A-661662	14-08-87	NONE	

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